Single-Agent High-Dose Cyclophosphamide for Graft-versus-Host Disease Prophylaxis in Human Leukocyte Antigen–Matched Reduced-Intensity Peripheral Blood Stem Cell Transplantation Results in an Unacceptably High Rate of Severe Acute Graft-versus-Host Disease

Kenneth F. Bradstock [1,*], Ian Bilmon [1], John Kwan [1], Kenneth Micklethwaite [1], Emily Blyth [1], Stephanie Deren [1], Angela Bayley [1], Val Gebski [2], David Gottlieb [1]

[1] BMT Service, Westmead Hospital, Sydney, New South Wales, Australia
[2] NHMRC Clinical Trials Centre, University of Sydney, Sydney, New South Wales, Australia

Article history:
Received 18 December 2014
Accepted 20 January 2015

Key Words:
Bone marrow transplantation
Peripheral blood stem cells
Allogeneic
Graft-versus-host disease
Prophylaxis
Cyclophosphamide

A B S T R A C T

High-dose cyclophosphamide given early after allogeneic hemopoietic cell transplantation has been shown to be effective prophylaxis against graft-versus-host disease (GVHD) in the setting of HLA-matched myeloablative bone marrow grafts, allowing avoidance of long-term immunosuppression with calcineurin inhibitors in some patients. Whether this approach is feasible using granulocyte colony–stimulating factor (G-CSF)–mobilized peripheral blood stem cell grafts is unknown. We conducted an exploratory phase 2 trial of cyclophosphamide given at 50 mg/kg i.v. on days 3 and 4 after transplantation as sole GVHD prophylaxis in recipients of G-CSF–mobilized peripheral blood stem cell grafts from HLA-matched related or unrelated donors after reduced-intensity conditioning therapy with fludarabine, carmustine, and melphalan. Five patients, ages 52 to 67 years, with high-risk hematologic malignancies were enrolled. Four of the 5 developed severe acute GVHD of grades 3 to 4, requiring treatment with methylprednisolone and cyclosporine; 3 were steroid refractory and were given salvage therapy. One of these 4 patients died of hepatic GVHD, one died of sepsis, and 2 survived. We conclude that post-transplantation cyclophosphamide is inadequate as sole GVHD prophylaxis in the context of peripheral blood reduced-intensity conditioning transplantations from HLA-matched donors. This trial is registered at ACTRN12613001154796.

INTRODUCTION

Graft-versus-host disease (GVHD) remains a major obstacle for the success of allogeneic hemopoietic cell transplantation. Despite decades of preclinical and clinical research, there is an ongoing risk of acute and chronic GVHD, even with full molecular matching for human leukocyte antigens (HLA) between donor and recipient. Prophylactic strategies include the use of calcineurin inhibitors, drugs that inhibit proliferating T lymphocytes, monoclonal and polyclonal antibodies against human T lymphocytes, and techniques to physically deplete the stem cell graft of donor T cells (recently reviewed in [1]). An alternative strategy developed at Johns Hopkins University is the use of high doses of cyclophosphamide early after stem cell infusion [2]. This is based on the premise that cyclophosphamide can delete alloreactive donor T lymphocytes, which are induced to proliferate soon after transplantation, thereby inducing tolerance [3]. Hemopoietic stem cells, which express high levels of the enzyme aldehyde dehydrogenase that is responsible for metabolism of cyclophosphamide, are resistant to the drug [4]. Recently, it has been shown that regulatory T cells, which play a role in inhibiting GVHD reactions, also have high aldehyde dehydrogenase levels when activated and are resistant to cyclophosphamide [5].

These observations led to clinical studies of GVHD prophylaxis using cyclophosphamide on days 3 and 4 after transplantation, either as a single agent in HLA-matched transplantations using bone marrow from relatives or volunteer unrelated donors [2,6], or with additional tacrolimus and mycophenolate mofetil in haploidentical related donor marrow transplantations [7]. These encouraging single-institution results led to a multicenter confirmatory study in the United States, where patients who received myeloablative conditioning therapy with fludarabine and intravenous busulphan and a bone marrow graft from an HLA-matched relative or unrelated donor were given 2 doses of cyclophosphamide on days 3 and 4 after transplantation as sole GVHD prophylaxis [8]. In 92 enrolled patients, the incidence of grades 3 and 4 acute GVHD was 15%, comparable with historical data using calcineurin inhibitor–based therapy.

Peripheral blood stem cell grafts, mobilized by granulocyte colony–stimulating factor (G-CSF) treatment of donors and collected by leukapheresis, are now widely used instead of harvested bone marrow, but have been shown in some studies to result in higher rates of acute and chronic GVHD [9-12]. The interaction between G-CSF–mobilized grafts and post-transplantation cyclophosphamide has not been widely studied. We and others have reported that post-transplantation cyclophosphamide, given with subsequent tacrolimus and mycophenolate mofetil, was effective in preventing serious acute GVHD in patients receiving

Financial disclosure: See Acknowledgments on page 943.

* Correspondence and reprint requests: Prof. Kenneth F. Bradstock, BMT Service, Department of Haematology, Westmead Hospital, Darcy Road, Westmead, NSW, Australia 2145.
E-mail address: ken.bradstock@sydney.edu.au (K.F. Bradstock).

1083-8791/
http://dx.doi.org/10.1016/j.bbmt.2015.01.020

Table 1
Patient Characteristics and Outcomes

Patient ID	Sex/Age, yr	Diagnosis	Donor	CD34 Dose, $\times 10^6$ per kg	CD3 Dose, $\times 10^6$ per kg	GVHD Onset, d	Organ/ Stage	Outcome
1426	F 56	AML CR1	MUD	6.0	146	NA	NA	Alive
1430	F 67	NHL CR1	MSD	6.0	119	90	S 3 GI 3	Dead
1438	F 67	AML CR1	MUD	5.0	224	34	GI 3 L 4	Dead
1439	M 52	AML REL1	MSD	5.4	238	27	S 2 GI 3 L4	Alive
1443	M 57	PH + ALL	MUD	4.2	183	21	S 2 L 4	Dead

F indicates female; AML, acute myeloid leukemia; CR1, first complete remission; MUD, matched unrelated donor; NA, not applicable; NHL, non-Hodgkin lymphoma; MSD, matched sibling donor; S, skin; GI, gastrointestinal; L, liver; M, male; REL1, relapse 1; PH + ALL, Philadelphia chromosome–positive acute lymphoblastic leukemia.

peripheral blood stem cell grafts from haploidentical relatives [13-16]. We therefore conducted a trial of post-transplantation cyclophosphamide as sole GVHD prophylaxis in patients receiving HLA-matched peripheral blood stem cell grafts. We chose a reduced-intensity conditioning regimen as this is the type most commonly used at our center, and we considered that only 1 regimen should be used for purposes of clarity.

PATIENTS AND METHODS

This was a prospective phase 2 clinical trial conducted at Westmead Hospital to evaluate the safety and efficacy of post-transplantation cyclophosphamide as GVHD prophylaxis in HLA-matched peripheral blood stem cell transplantations. The trial was approved by the human research ethics committee of the Western Sydney Local Health District and is registered at ACTRN12613001154796. All patients provided written consent after reading an approved information form. Eligibility criteria consisted of patient ages between 15 and 70 years, a diagnosis of high-risk hematological malignancy requiring allogeneic hematopoietic cell transplantation, availability of either a fully HLA-matched sibling donor (matched for HLA-A, -B, and -DRB1) or an unrelated donor matched at allele level for HLA-A, -B, -C and -DRB1, absence of serious organ dysfunction, and negativity for HIV and hepatitis B and C.

Reduced-intensity conditioning therapy consisted of fludarabine 30 mg/m^2 i.v. daily for 4 days on days −5 to −2, carmustine 200 mg/m^2/day i.v. (adjusted to 150 mg/m^2/day for patients 55 years of age and over) for 2 days on days −4 and −3, and melphalan 140 mg/m^2 i.v. (adjusted to 110 mg/m^2 for patients 55 years and over) on day −1, as previously described [17,18]. An unmanipulated G-CSF–mobilized peripheral blood stem cell graft from an HLA-identical donor was given on day 0. Cyclophosphamide 50 mg/kg was given i.v. on days +3 and +4, together with equivalent doses of mesna administered 1 hour after each cyclophosphamide dose. No other GVHD prophylaxis was given. Patients were managed in the outpatient clinic during conditioning therapy and only admitted after transplantation for management of complications. Supportive care consisted of transfusions with red cell and platelet concentrates, pretransplantation ganciclovir i.v. from day −8 to −4 if cytomegalovirus (CMV) seropositive, then monitoring with PCR on blood and pre-emptive ganciclovir if CMV viremia occurred, cotrimoxazole from day −9 to −2 before transplantation for *Pneumocystis jiroveci* prophylaxis, and acyclovir 800 mg twice daily and fluconazole 400 mg daily as herpes virus and yeast prophylaxis, respectively.

Acute GVHD was diagnosed on clinical grounds and histopathological examination of affected tissues and staged according to modified Keystone criteria [19]. Treatment of acute GVHD consisted of i.v. cyclosporine 1.5 mg/kg every 12 hours and i.v. methylprednisolone 2 mg/kg daily. Patients failing to respond after 7 to 14 days were given salvage therapy with horse anti–T cell globulin (ATGAM [Pfizer, New York, NY]) 15 mg/kg daily for 5 days and etanercept 25 mg subcutaneously twice weekly for 4 weeks.

The design of the study was an exploratory phase 2 trial, with a projected accrual of 24 patients over 2 years. The primary study endpoint was the rate of grades 3 and 4 acute GVHD occurring by day 100 after transplantation, with secondary endpoints being the rate of all grades of acute GVHD, the requirement for additional immunosuppression, the incidence of chronic GVHD, relapse rate, treatment-related mortality at 100 days and at 1 and 2 years, and overall and progression-free survival at 2 years. The trial was monitored by an independent committee. The stopping rules for the trial were based on an historical observed rate of grades 3 and 4 acute GVHD of 13% for HLA-matched transplantations, using the same conditioning regimen and GVHD prophylaxis with rabbit antithymocyte globulin (Fresenius, Sydney, Australia), cyclosporine, and mycophenolate mofetil. The protocol called for a review of data every three months by the monitoring committee and closure of the study if 4 or more cases of grades 3 or 4 acute GVHD were observed in the first 12 patients enrolled. This boundary is based on the charts of Mehta and Cain [20], and is consistent with a 95% confidence of an underlying rate of grades 3 and 4 GVHD of 13% or lower [20]. Otherwise, accrual would proceed to 24 patients.

RESULTS

A total of 5 patients were enrolled on this trial between July and October 2014 before its early closure. Demographic and disease details are given in Table 1. There were 3 females and 2 males, ages 52 to 67 years (median, 57 years) at transplantation. Diagnoses were acute myeloid leukemia (n = 3), Philadelphia chromosome–positive acute lymphoblastic leukemia (n = 1), and high-grade non-Hodgkin lymphoma (n = 1). All were in morphological remission at the time of transplantation, except for patient 1439 who underwent transplantation in early untreated first relapse of acute myeloid leukemia. All patients and their donors were CMV-seropositive, except for patient 1439, who was seronegative with a seronegative unrelated donor. Stem cell grafts contained 4.2 to 6.0 $\times$ 10^6 CD34$^+$ cells/kg (median, 5.4) and 119 to 238 $\times$ 10^6 CD3$^+$ cells/kg (median, 183).

All patients engrafted, with median times to neutrophil counts of .5 and 1.0 $\times$ 10^9/L of 18 (range, 15 to 26) and 22 (range, 16 to 27) days, respectively, and median time to platelet count 20 $\times$ 10^9/L of 29 (range, 17 to 41) days. All 5 patients required admission for treatment of post-transplantation complications, including 2 with brief admissions to the intensive care ward for treatment of sepsis and hypotension. The first patient enrolled had no evidence of acute GVHD when evaluated on day 100 after transplantation and required no additional immunosuppression. However, the subsequent 4 patients developed acute GVHD at 21 to 90 days (median, 30 days) after transplantation. Three had skin involvement, 3 had gastrointestinal involvement, and 3 had hepatic disease. All were confirmed on biopsies of affected organs, including 2 by transjugular liver biopsy. One patient (1430) had concurrent relapse of high-grade lymphoma, confirmed on mediastinal lymph node biopsy.

Patient 1430 developed a rash and diarrhea on day +90, and this patient was started on cyclosporine and methylprednisolone 2 mg/kg daily on day 93. There was improvement in the rash, but there was persistent diarrhea, and the patient died of septicemia on day 102. Patient 1438 had vomiting and diarrhea on day +34 and was started on methylprednisolone 2 mg/kg on day +37, with cyclosporine being added on day +41. There was progression of GVHD and salvage therapy was started on day +51; however, there was no response and the patient died on day +80. Patient 1439 presented with rash on day +27 and was started on methylprednisolone 2 mg/kg on day + 31. Cyclosporin was added

on day +35 when the serum bilirubin became elevated, and salvage therapy started on day +47, when there was further progression. The patient responded and is alive at day + 120. Finally, patient 1443 had a rash and elevated bilirubin at day +31. He was given methylprednisolone 2 mg/kg on day +33, with cyclosporine being added at day + 44. The bilirubin continued to rise and salvage therapy was started on day +50. He failed to respond and died of liver failure on day 100.

In view of the occurrence of 4 cases of severe acute GVHD in the first 5 cases treated on this protocol, the trial monitoring committee recommended closure of the study. Based on a 13% failure rate, the probability of 4 failures in the first 5 cases is .0012, and to be consistent with a 13% failure rate over the whole trial would require at most 2 failures in the next 19 patients (based on the upper 1-sided 95% confidence interval for a binomial proportion), which was considered to be highly unlikely.

DISCUSSION

This clinical trial demonstrates that post-transplantation high-dose cyclophosphamide is inadequate as sole GVHD prophylaxis in the context of the use of G-CSF–mobilized peripheral blood stem cell grafts from HLA-matched related or unrelated donors after reduced-intensity conditioning therapy. The high rate of severe acute GVHD observed mandated closure of the study and contrasts with the outcome reported recently in a multicenter setting where post-transplantation cyclophosphamide was studied using bone marrow rather than G-CSF–mobilized blood as the stem cell source [8]. The conditioning therapy used in that trial was essentially myeloablative, with 4 doses of i.v. busulphan being given, rather than reduced intensity as in our study. We cannot exclude the possibility that the choice of regimens was a factor in the major difference in rates of severe acute GVHD observed in the 2 studies. However, although the onset of acute GVHD may be delayed after reduced-intensity transplantations [21], there is no convincing evidence to suggest an increased risk of acute GVHD compared with that of myeloablative regimens [22]. It is more likely that the difference in the rate of grades 3 and 4 acute GVHD was due to the type of stem cell product used. G-CSF–mobilized blood stem cell products typically contain at least 10-fold higher numbers of $CD3^+$ donor lymphocytes than marrow, increasing the risk of both acute and chronic GVHD.

The impact of the use of G-CSF–mobilized blood on GVHD risk has been most extensively studied in the context of myeloablative conditioning therapy. A meta-analysis of 9 randomized trials comparing bone marrow with mobilized blood in matched sibling transplantations showed no difference in acute GVHD of all grades between the 2 stem cell sources, but an increased rate of grades 3 and 4 acute GVHD in the peripheral blood group was observed, with an odds ratio of 1.39 [9]. In contrast, in a large retrospective registry study, whereas peripheral blood grafts conveyed higher risks of acute GVHD grades 2 to 4 as well as 3 and 4 in patients under 40 years of age, the converse was true in older patients, with bone marrow being associated with higher GVHD risk [23]. In transplantations using matched unrelated donors, a registry study showed higher rates of grades 2 to 4 acute GVHD with peripheral blood grafts, although the rate of severe grades was similar between blood and bone marrow groups [10]. In a more recent registry analysis examining the interaction between a number of clinical variables, in particular graft source and conditioning intensity, peripheral blood grafts from matched siblings had a lower risk of acute GVHD grades 2 to 4 than bone marrow for patients receiving reduced-intensity regimens, whereas for unrelated donor grafts, the converse was true [11]. These studies generally support the notion of an increased risk of acute GVHD with peripheral blood grafts, although other variables such as donor type, conditioning intensity, and GVHD prophylaxis influence outcomes.

Recently, Solomon et al. from Atlanta reported a small single-center study in HLA-matched transplantations using myeloablative conditioning therapy and G-CSF–mobilized blood stem cell grafts [24]. GVHD prophylaxis consisted of post-transplantation cyclophosphamide followed by sirolimus, with no calcineurin inhibitor or other agents. Rates of acute GVHD grades 2 to 4 and grades 3 and 4 were 46% and 15%, respectively, and chronic GVHD occurred in 31%. A switch to tacrolimus was required in 31%. The authors concluded that post-transplantation cyclophosphamide followed by single-agent sirolimus provided adequate GVHD prophylaxis, without the need for calcineurin inhibitor therapy.

Finally, it should be noted that post-transplantation cyclophosphamide followed by tacrolimus and mycophenolate provides adequate protection against severe acute GVHD in haploidentical related transplantations, even with the use of peripheral blood grafts. We conclude that the use of additional prophylactic agents, such as tacrolimus or sirolimus, will be necessary to provide adequate immune suppression if post-transplantation cyclophosphamide is to be used with HLA-matched peripheral blood stem cell grafts.

ACKNOWLEDGMENTS

The authors thank Professor Mark Hertzberg and Associate Professor Howard Gurney for their assistance in monitoring the trial.

Financial disclosure: The authors have nothing to disclose.

Conflict of interest statement: The authors have no conflicts of interest to disclose.

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Cytochrome *P450 2B6*5* Increases Relapse after Cyclophosphamide-Containing Conditioning and Autologous Transplantation for Lymphoma

Veronika Bachanova [1,*], Ryan Shanley [1], Farhana Malik [1], Lata Chauhan [2], Vishal Lamba [2], Daniel J. Weisdorf [1], Linda J. Burns [1], Jatinder Kaur Lamba [2]

[1] *Blood and Marrow Transplant Program, University of Minnesota, Minneapolis, Minnesota*
[2] *Department of Pharmacotherapy and Translational Research, College of Pharmacy, University of Florida, Gainesville, Florida*

Article history:
Received 17 November 2014
Accepted 3 February 2015

Key Words:
Non-Hodgkin lymphoma
Hodgkin lymphoma
Autologous hematopoietic cell transplantation
Cyclophosphamide
Cytochrome P450
polymorphism

A B S T R A C T

Cyclophosphamide (Cy) is a prodrug that depends on bioactivation by hepatic cytochrome P450 (CYP) enzymes for its cytotoxicity. We evaluated the influence of single nucleotide polymorphisms (SNPs) of CYP enzymes on the efficacy of autologous hematopoietic cell transplantation (HCT) for lymphoma. SNPs of 22 genes were analyzed in 93 patients with Hodgkin (n = 52) and non-Hodgkin lymphoma (n = 41) treated with high-dose Cy followed by autologous HCT between 2004 and 2012. Preparative regimens contained Cy (120 mg/kg) combined with carmustine/etoposide (n = 61) or Cy (6000 mg/m^2) with total body irradiation (n = 32). Lack of complete remission as measured by pretransplant positron emission tomography was the sole clinical factor associated with increased risk of relapse (HR, 2.1). In genomic analysis, we identified a single SNP (rs3211371) in exon 9 (C > T) of the *CYP2B6* gene (allele designation 2B6*5) that significantly impacted patient outcomes. After adjusting for disease status and conditioning regimen, patients with the *CYP2B6*1/*5* genotype had a higher 2-year relapse rate (HR, 3.3; 95% CI, 1.6 to 6.5; $P = .041$) and decreased overall survival (HR, 13.5; 95% CI, 3.5 to 51.9; $P = .008$) than patients with the wild-type allele. Two-year progression-free survival for patients with 2 hypofunctional *CYP2B6* variant genotypes (*5 and *6) was only 11% (95% CI, 1% to 39%) compared with 67% (95% CI, 55% to 77%) for patients with the wild-type *CYP2B6*1* allele in exon 9. Our results suggest that *CYP2B6* SNPs influence the efficacy of high-dose Cy and significantly reduce the success of autologous HCT for lymphoma patients with the *CYP2B6*5* variant.

INTRODUCTION

High-dose chemo-/radiotherapy with autologous hematopoietic cell transplantation (HCT) often cures patients with recurrent chemotherapy-sensitive lymphoma. Although most patients attain remission after autologous HCT, disease progression is the most common cause of treatment failure,

Financial disclosure: See Acknowledgments on page 947.

* Correspondence and reprint requests: Veronika Bachanova, MD, PhD, Blood and Marrow Transplant Program, University of Minnesota, Mayo Mail Code 480; 420 Delaware Street SE, Minneapolis, MN 55455.
E-mail address: veronikabachanova@msn.com (V. Bachanova).

1083-8791/
http://dx.doi.org/10.1016/j.bbmt.2015.02.001